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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/121,798 | 07/23/1998 | ROBERT BRIDENBAUGH | 018484-00120 | 3701 |

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| EXAMINER | |
|---|---|
| VOGEL, NANCY S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: ~~07/28/2005~~ 7/22/06

Remail

**Please find below and/or attached an Office communication concerning this application or proceeding.**

PTO-90C (Rev. 10/03)

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/121,798 | BRIDENBAUGH ET AL | |
| | Examiner | Art Unit | |
| | Nancy T. Vogel | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *23-26 and 28-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26 and 28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



5.02

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/26/05 has been entered.

Claims 23-26 and 28-47 are pending in the case.

Receipt of the Information Disclosure Statement on 2/24/05 is acknowledged.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 23, 33, 37, 43, and by dependence, claims 24-32, 34-36, 38-42, and 44-47, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed: "a series of filters including at least one glass fiber filter and at least one

nylon filter", before and/or after the step of contacting the solution comprising plasmid DNA with a TMAE anion exchange chromatography resin (claims 23, 33, 37, 43). It is noted that the phrase "at least one" includes an unlimited upper range limit. This a new matter rejection. The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned limitations, as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112..

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

Claims 23-26, 27-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Nochumson et al. (US Pat. Appl. No. US 2001/0034435 A1), in view of Wan et al. (US Pat. No. 5,837,529) Lee et al. (US Pat. No. 6,197,553), Lee et al. (US Pat. No. 6,197,553), Song et al. (J. Chem. Soc. Faraday Trans. 1995, 91(19), 3389-3398) (all of record) and Consolazio et al. (US Patent 4,374,063) (newly cited).

Nochumson et al. disclose a method for purifying plasmid DNA comprising: a) lysing cells with alkaline conditions, b) removal of precipitated proteins, chromosomal DNA and cell debris (paragraphs 0049, 0074-0075), c) filtration (paragraph 0076), d) contacting a solution comprising plasmid DNA with a trimethylamino ethyl (TMAE) anion exchange chromatography resin, the solution having a conductivity at which the plasmid DNA is bound to the resin e) washing the resin and f) eluting the plasmid DNA with a step or continuous gradient of increasing conductivity (paragraph 0077) g) ultrafiltration/diafiltration followed by sterile filtration (paragraph 0079) (see page 4, paragraphs 0041 – 0045, Fig. 3, page 6, paragraphs 0074-0080, claims 18-27.). The reference discloses that the lysis solution and precipitation/neutralization solution is mixed with the cells by flowing through in-line static mixers (paragraph 0084).

The difference between the reference and the claims is that the reference does not disclose the use of at least one glass fiber filter and at least one nylon filter prior to anion exchange chromatography, RNAse is not used, and the step of purifying using ultrafiltration in the presence of a gel layer is not specified.

However, Lee et al. disclose a method of plasmid purification in which RNAse is used to eliminate RNA prior to filtration and anion exchange purification (paragraph bridging col. 2-3). Two filtration steps of the lysate are disclosed (col. 7, lines 5-10). Filtration as a final step using membranes having a pore size of, for example 0.2 microns and smaller, is also disclosed (column 6, lines 27-33). Wan et al. disclose a method for purifying large quantities of plasmid DNA for pharmaceutical use by mixing a solution of bacterial cells comprising plasmid DNA with an alkaline lysis solution by

flowing through a first static mixer to obtain a lysate, and contacting the lysate with a precipitating solution by flowing through a second static mixer, thereby forming a precipitation mixture (see abstract, figures, and col. 2-4). The precipitation solution is potassium acetate (col. 4, line 23-24), and the lysing solution is alkaline (col. 4, lines 17-19). Wan et al. disclose filtering the lysate through membrane filter to remove insoluble materials, and subjecting the filtrate to ultrafiltration to remove impurities (see col. 1, lines 42-54). The reference discloses that the material of the membrane filter may be any commercially available filter, preferably with a pore size of 0.1-0.2 um. (col. 2, lines 38-46). Song et al. disclose that the process of ultrafiltration involves the development of a polarization layer of the solute on the ultrafiltration membrane, which provides a resistance to flow through the ultra filter. The presence of this layer provides a gel layer through which all other solute must pass (see page 3390, col. 2, Figs. 1 and 2, and page 3394, col. 1, and discussion at page 3396, col. 2). Consolazio et al. disclose the use of Pall Ultipor filters for the removal of endotoxins from solutions (see column 3, lines 26-30).

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the method for purifying plasmid DNA from such impurities as endotoxin, with the steps from methods for purifying plasmid DNA disclosed by Wan et al., Lee et al., and Consolazio et al., because they were all involved in the process of purifying large quantities of plasmid DNA for pharmaceutical use, or generally in the removal of impurities from solutions. One would have been motivated to do so by the disclosed advantages of such steps as RNAse treatment

(removal of RNA molecules, an impurity), filtration (removal of debris impurities), and ultrafiltration (removal of impurities). Song et al. provides the theoretical background teaching that a gel layer would be present in an ultrafiltration process.

Applicants have argued in their response received 2/24/05, that this combination of references (without the Consolazio et al. reference, which is newly cited) is improper since the use of at least one glass filter and at least one nylon filter is not taught by the references, and further, there is no suggestion in the art to combine filtration using these filters with the method of purification using TMAE anion exchange chromatography. However, as has been stated above, the Lee reference discloses two filtrations steps using filters which are known in the art, which would clearly include glass and nylon filters. In addition, as has been stated above, the reference which discloses TMAE anion exchange chromatography, i.e. Nochumson et al., also discloses that the well known step of filtration may be additionally used. It is further noted that Nochumson et al. states that "Steps 9 and 10 are ultrafiltration/diafiltration and sterile filtration to yield the final product. These are common procedures that may be insubstantially modified by those skilled in the art without departing from the scope of the invention" (page 6, paragraph 0073). These teachings refute applicant's arguments that the use of filtration was not taught or suggested by the art. The use of the commercially available glass and nylon filters, which were well known in the art for filtering out impurities, would have been obvious to one of ordinary skill in the art. All of the cited references have the goal of purification of plasmids, except for Consolazio which provides the general teaching that the Pall Ultipor filter is useful for filtering out endotoxins, and all disclose steps

which would have been expected, when combined with any of the other teachings, to further purify the plasmid from cellular contaminants. For these reasons, the rejection is maintained.

Claims 23-26, and 28-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Nochumson et al. (US Pat. Appl. No. US 2001/0034435 A1), in view of Wan et al. (US Pat. No. 5,837,529) Lee et al. (US Pat. No. 6,197,553), and Song et al. (J. Chem. Soc. Faraday Trans. 1995, 91(19), 3389-3398) and Consolazio et al. (US Patent 4,374,063) as applied to claims 23-26, and 28-43 above, and further in view of The Pall ULTIPOR $^{R}$ N66$^{R}$ Membrane Filter Guide (ref. C20, cited on the Information Disclosure Statement filed 2/24/05).

Nochumson et al., Wan et al., Lee et al. ('553), Song et al. and Consolazio et al. are cited for the reasons set forth above. The difference between the references and the instant claims is that the nylon filter used is an N66 filter.

However, The Pall ULTIPOR N66 Membrane Filter Guide discloses commercially available N66 nylon filters, and discloses their use for removing impurities and sterilization (see pages 1-6). It would have been obvious to one of ordinary skill in the art to have utilized such well known, commercially available filters as the N66 nylon filter produced by Pall (ULTIPOR), in order to remover impurities from any solution of interest, including a plasmid containing bacterial lysate solution. One would have been motivated to do so by the teaching of Nochumson et al. that variations on the commonly known step of sterile filtration would have been useful to add to the method of plasmid purification disclosed therein, and by the teachings of the secondary references which

teach the use of nylon or glass filtration for the purpose of removing impurities, including endotoxins, from biological solutions. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NANCY VOGEL, PH.D.
PATENT EXAMINER

N. Vogel
Patent Examiner